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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/822,672	HANNA, NABIL	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-96* is/are pending in the application.

4a) Of the above claim(s) *1-73,80 and 88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *74-79,81-87 and 89-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8-10
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of group X, Claims 74-75 in Paper No. 6 and 9 is acknowledged with the species of an anti-CD20 antibody. The traversal is on the ground(s) that claims 72-86 should be examined together since all require the administration of an anti-IL-10 antibody and a B cell depleting antibody. This is found partially persuasive. Claims 72 to 73 do not require a B cell depleting antibody and as such is a distinct method as stated in the restriction requirement. Claims 74-75 will be rejoined with claims 76-86 for examination. The rest of the restriction requirement is maintained as stated in the restriction requirement and the response filed 7/25/02 and 10/9/02 did not address the rest of the restriction requirement.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-73, 80, 88, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction (election) requirement in Paper No. 6.

3. Claims 74-79, 81-87, 89-96 are under examination with the species of an anti-CD20 antibody.

Specification

4. The disclosure is objected to because of the following informalities:

The use of the trademark "Rituximab", RITUXAN", "BEXXARTM", "CYTOXANTM", and others has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 81, 82, 84, 86, 90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 81, 82, 84, 86, and 90 contains the trademark/trade name "RITUXAN". Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade

name is used to identify/describe an anti-CD20 antibody and, accordingly, the identification/description is indefinite.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 81, 82, 84, 86, and 90 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line which produces an antibody having the exact chemical identity of "RITUXAN" is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species RITUXAN. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

9. Claims 81, 82, 84, 86, and 90 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating B cell lymphoma in a patient by administration of the anti-CD20 antibody C2B8, with the appropriate evidence of public availability (see above), does not reasonably provide enablement for a method comprising administration of RITUXAN. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in

the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method of treatment of B cell lymphoma with RITUXAN. The specification enables a method for treatment of B cell lymphoma with a C2B8 antibody. The specification does not enable a method with RITUXAN.

The specification discloses the RITUXAN is rituximab which is the C2B8 antibody directed to CD20 (see page 25, lines 21-23). The trade name RITUXAN comprises an antibody to CD20. Since it is unclear (see 112 second rejection above) what is encompassed by the trade name RITUXAN, one skill in the art would not know how to use the claimed invention. It is not clear what components or formulations are encompassed by RITUXAN or if this composition has changed over time or will change in the future to encompass other antibodies or components. Thus, since it is unclear what is encompassed by the term "RITUXAN", one skill in the art would be forced into undue experimentation to practice the broadly claimed invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 74-79, 81-87, 89--96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alas et al (Blood 92:601A, 1998) and further in view of Levy et al (J. Clin Invest 93:424-428, 1994) and Goldenberg (US Patent 6,183,744, filed 3/1998) and as evidenced by the specification.

The claims recite a method of treating non-Hodgkin's lymphoma in a patient with an anti-IL10 antibody and humanized Rituxan antibody and chemotherapy with CHOP wherein the antibodies are administered intravenous and the dose rages from 0.01 to 1000 mg/Kg.

Alas et al teach the use of the C2B8 antibody which as evidenced from the specification on page 25, lines 20 to page 26, line 11, C2B8 is RITUXAN and is the humanized or chimeric form of the anti-CD20 antibody. Alas et al teach the addition of IL-10 to C2B8 treated 2F7 cells which are non-Hodgkin's lymphoma cells resulted in decreased sensitivity of the cell to sensitized agents and IL-10 has been shown to function as a resistance factor and protect tumor cells from the cytotoxic effects of therapeutic drugs and involvement of bcl-2 could explain the resistance involved. Alas et al does not teach an anti-IL-10 antibody or addition of a chemotherapeutic agent such

as CHOP. These deficiencies are made up for in the teachings of Levy et al and Goldenberg.

Levy et al teach an anti-IL-10 antibody and its effects on apoptosis. Specifically Levy et al teach the Bcl-2 protein prolongs the survival of a cell by blocking programmed cell death and in humans inappropriate expression of the bcl-2 oncogene has been implicated in lymphoma and addition of the anti-IL-10 antibody abolishes this effect and showed that IL-10 was responsible for the upregulation of bcl-2 expression (see page 427).

Goldenberg teach multimodal therapy with antibodies and chemotherapeutic agents such as CHOP and the antibodies are administered intravenous at various doses of mg per patient (see column 13-14).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of treating non-Hodgkin's lymphoma by administering the Rituxan antibody and an anti-IL-10 antibody in combination with chemotherapy.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method of treating non-Hodgkin's lymphoma by administering the Rituxan antibody and an anti-IL-10 antibody in combination with chemotherapy because Alas et al teach treating 2F7 cells with C2B8 and treatment leads to sensitation to chemotherapeutic drugs and IL-10 has been shown to function as a resistance factor and protects tumor cells from cytotoxic effects of drugs. In addition, one of ordinary skill in the art would have been motivated to and

had a reasonable expectation of success to have produced a method of treating non-Hodgkin's lymphoma by administering the Rituxan antibody and an anti-IL-10 antibody in combination with chemotherapy because Levy et al teach anti-IL-10 antibodies abolish the effect of Bcl-2 on apoptosis thus leading to cell death. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method of treating non-Hodgkin's lymphoma by administering the Rituxan antibody and an anti-IL-10 antibody in combination with chemotherapy because Goldberg teach combination therapy of an antibody and a chemotherapeutic to treat B-cell malignancies. Therefore, it would have been obvious to combine an anti-IL-10 antibody wherein removal of IL-10 results in abolishing the effects of bcl-2 by blocking cell death and adding C2B7 to sensitize the 2F7 cells and adding a chemotherapeutic because combination therapy has been shown to treat cancers effectively.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879